Clinical Proceedings

of the

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

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CLINICAL PROCEEDINGS OF THE CHILDREN'S HOSPITAL

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Occasionally, the remarks and observations of guest speakers are included in this bulletin when thought to have particular interest. The proximity of the Children's Hospital to the Medical Centers of the Army, Navy and United States Public Health Service affords us the opportunity to invite many distinguished physicians to our conferences.

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Special Report

TRAUMATIC HEAD INJURIES IN INFANTS AND CHILDREN

A Five Year Review of 323 Cases at The Children's Hospital, Washington D. C.

Dr. Elizabeth Linson

The purpose of this paper is to review the cases of acute cranial trauma admitted to this hospital during the past five years. There were 323 admissions from September 1, 1940 to September 1, 1945 and these comprised 1.02% of the total hospital admissions during this period. The duration of hospitalization was short, the majority of patients being under observation for 24–48 hours. The average hospital stay was 4.8 days. Of the total number 167 were white and 156 colored. The ratio of males to females was approximately 2:1.

In reviewing the age incidence we find that 8% or 28 patients were between one and twelve months of age. In this group the accidents may be said to be due mainly to carelessness on the part of the parents. The majority of cases occurred in the next few years of life during the period when the child has learned to walk and explore his surroundings and before the ability to reason has developed. About 50% of the accidents occurred between the ages of one and six years.

History

A history of a fall was obtained in 75% or 242 cases. Most of the falls occurred during play (81) and were caused by the child's tripping or running into another child. In 71 cases the falls were from a height greater than 6 feet, many of them being from 2nd and 3rd story porches or windows. Others included falls from moving cars (14), down steps (35), from the high chair or crib and from an adult's arms. In 42 cases the child was knocked down by a moving vehicle, i.e. a car, bus or bicycle. Sixteen were injured by thrown objects such as rocks or toys and one by a goldfish bowl filled with water which fell from a 2nd story window. Two were birth injuries following forceps delivery.

Of particular importance in the history is the detailed description of symptoms following the accident and the time after injury at which they developed. Loss of consciousness is considered the most important symptom in determining the type and severity of cerebral damage. This symptom occurred in 120 of the cases. There was no loss of consciousness in 183 and in 20 no reference to this symptom was made in the history.

A more detailed study was undertaken of the presenting symptoms and

their time of onset in a group of 187 cases. Sixty-one children had a history of loss of consciousness. The duration of this period was from a few seconds to minutes in approximately one-half of this group, from one-half to one hour in 7, several hours in 3 and 36 hours in one case. In those whose comatose state lasted several hours to days we have evidence of severe brain damage or cerebral edema. Ninety per cent of these children lost consciousness immediately after the injury, six after a few minutes and one after 4 hours. The last case illustrates the importance of determining the presence of a lucid or symptom-free interval with later development of coma, since this history when present is characteristic of an extra-dural hematoma which was found to be present in this child at operation.

Other symptoms associated with cerebral injury are shown on chart 1 in the order of their frequency. Vomiting, drowsiness and headache were the most common. Bleeding from the ears and nose was present in 14 of the

PRESENTING SYMPTOMS

Loss of consciousness	120
No loss of consciousness	183
Not stated	20
Other symptoms (187 cases)	
Vomiting	63
Drowsiness	36
Headache	19
Bleeding from ears and nose	14
Mental confusion	11
Convulsions	7
Ataxia	2
Dizziness	1
Cyanosis	1

FIG. 1

cases and in 4, a fracture was demonstrated in an adjacent area of the skull. A basal fracture was present in 2 with epistaxis and fracture of the nasal bones in one. In contrast to the loss of consciousness, 90% of these symptoms were delayed in onset, developing from several minutes to hours following the accident. The delay in onset suggests their occurrence as a sign of developing cerebral edema and increasing intra-cranial pressure.

CLINICAL

Positive neurological signs were present in 211 of the cases reviewed. For the most part these consisted of hyperactive or hypoactive deep reflexes. In addition to generalized changes in reflexes, localized changes were noted in a few. The Babinski test was positive in 8 and unilateral in one-half of these. Additional signs of damage to the motor area and pyramidal system included hemiplegia, hemiparesis, and spasticity of local muscle groups.

These signs and their persistance or resolution are of marked importance in evaluating the severity of brain damage, whether cerebral edema alone exists or whether a contusion or laceration is present which may be followed by scarring and permanent disability.

Positive eye signs were noted in about 20 cases. These included inequality of pupils, dilatation of pupils, failure to react to light, weakness of the external recti muscles and indistinct discs on eye ground examination. A fixed and dilated pupil has been stressed as an important diagnostic and localizing sign in extradural hematomata. This was present in the case of extra-dural hematoma in our series.

The hospital course can best be followed by clinical observation of the depth or changes in state of consciousness, changing neurological signs, and recordings of the blood pressure, pulse rate, temperature and respiration. Increasing depth of coma is an important sign of breaking in compensation and increasing intracranial pressure. This finding was evident in the deaths in our series.

Measurements of blood pressure, pulse rate, temperature and respiration are reliable objective signs and enable the observer to easily detect slight changes in the patient's condition. The blood pressure was checked in 50% of the cases. In mild concussion the levels of pressure were fairly stable. Elevations above 120 systolic were recorded in 19 cases but these rarely lasted more than 24 hours. In severe concussions and contusions on the other hand repeated readings showed a fluctuation of 10 mm. and more with systolic pressure over 120 in 9 cases and persisting for several days. The fluctuations of pressure with falls to shock level were present in a few cases of cerebral laceration and necessitated frequent readings and the use of plasma when indicated. The pulse rate followed a similar course being elevated for 12–24 hours in mild injuries with rates over 120 in 96 patients. In 16 with severe injuries the rate remained for more than 24 hours above 120, 8 cases ranging between 140–160/min. Elevations in temperature above 100° were noted in 66 cases. Sustained high fever was seen in severe brain damage and in the presence of intracranial infection. Respirations were noted to increase above 30/min. in only 10 patients and showed marked depression only terminally in the development of Cheyne-Stokes respiration.

The one case of sub-dural hematoma in our series represents an interesting hospital course. This 7 year old child was stuporous on admission and a definite history was not available. Blood pressure on admission was 100/65 and rose to 120/60 in six hours, subsequently falling to normal by the third day and at that time the child had become fairly alert. Spinal fluid pressure was then 4 mm. Hg. On the seventh hospital day convulsions occurred involving the right side. The blood pressure was taken and showed a rise to 150/70. Pulse rate had dropped to 70. Spinal fluid pressure was

15 mm. Hg. Neurological examination revealed a right hemiplegia. The child was operated on and a subdural hematoma evacuated. The postoperative course was uneventful with a disappearance of neurological signs and a fall in blood pressure to 90/60.

Diagnosis

Of the total admissions, 172 were diagnosed as cerebral concussion, 113 cerebral contusion and 7 cerebral laceration. The criteria for diagnosis of concussion were the presence of one or more of the symptoms listed previously, rapid clearing of these symptoms, and no signs of residual central nervous system damage. Histologically there are no changes in the brain tissue. Under cerebral contusion we included those who in addition to symptoms of concussion showed signs of subarachonid bleeding, localization of neurological signs and those whose hospital course was relatively stormy with symptoms of increased intracranial pressure lasting more than 24 to 48 hours. Cerebral contusions have been described histologically as petechial hemorrhages or perivascular hemorrhages with coexisting cerebral edema. Cerebral laceration was the diagnosis in those with evidence of severe damage, subarachnoid hemorrhage, whose blood pressure and pulse readings showed wide fluctuations from increased intracranial pressure to shock levels and whose neurological signs revealed marked local or generalized damage.

Of particular importance in consideration of head injuries in children is the rarity of massive intracranial hemorrhages. There was one case of an extradural hematoma and one of a subdural hematoma, the incidence of each being 0.3%. The incidence of extradural hematoma in adults has been reported as 3% by Munroe and 1.3% of 307 cases from Boston City Hospital. A review of autopsies in adults by Levinson reported incidence of 11% and 54% of extradual and subdural hematomata, respectively. Though this is not a comparable series it does represent a higher frequency of intracranial hemorrhages in adults. This has been explained by the greater elasticity of the blood vessels in children and by the location of the middle meningeal artery in children as being adjacent to rather than embedded in the temporal bone.

Procedures used to assist in diagnosis consisted mainly of x-rays and lumbar punctures. X-rays were taken in 255 cases revealing a fracture present in 83 or 32% of the patients. The parietal bone was the most frequent site of fracture occurring in 56 cases, the frontal bone in 14 and the occipital bone in 19. Extension from one to another was present in a few of these and extension into the base in 2 patients. Twenty-six lumbar punctures were done. There were signs of subarachnoid bleeding in 9 cases and infection in 2 cases. Urinalyses were done in 218 cases and

showed the presence of acetone in 24% of these. This evidence of acidosis is an important point to be considered in the treatment of the patient. Another debatable diagnostic point is the presence of sugar in the urine, a finding in several of our cases which is said to be evidence of injury in the region of the third ventricle. Because of the importance of these findings urinalyses should be done routinely on admission.

Complications

Two important complications to be considered are brain abscess and meningo-encephalitis. In our series there was one definitely proven case of each. The brain abscess was secondary to a compound depressed fracture of the skull in an 8 year old child who had been treated at another hospital for laceration of the scalp. Fragments of bone were embedded in the brain tissue. The boy recovered after prolonged hospitalization for drainage of the abscess and treatment of secondary osteomyelitis of the skull.

The other case was that of a 14 year old boy diagnosed as fracture of the cribiform plate from a history of epistaxis and a profuse clear serous nasal discharge occurring after a fall out of a tree. Signs of meningo-encephalitis developed by the second day after injury and on admission Pneumococcus type XIX was recovered from the spinal fluid. The history revealed also that the boy had received gr. $\frac{1}{8}$ of morphine by his private doctor before admission. It is possible that this contributed to his rapid death. The child expired after a few hours, despite treatment with penicillin and sulfadiazine.

Treatment

Conservative therapy is the treatment to be strictly adhered to in 99% of head injuries in children. As Grant briefly states, the only indication for early operative intervention is the prevention of meningitis and the relief of increasing intra cranial pressure due to the presence of a rapidy expanding mass lesion. The rare occurrence of such lesions in children reduces the necessity for operation to a minimum.

A review of the types of conservative therapy used was made and certain recommendations can be made from this study. Bed rest was the only treatment necessary in 138 cases. In those who presented signs of increased intracranial pressure a variety of methods was used and by far the commonest were dehydrating measures employed in an attempt to decrease cerebral edema. Fluids were limited to less than 500 c.c. per 24 hours in 81 cases. Hypertonic glucose (50%) was given intravenously in seven cases. Magnesium sulfate was administered orally in 20 and parenterally in 4 cases. The indication of these measures should be questioned in so far

as ¼ of the patients on whom urinalyses were done showed evidence of dehydration and acidosis on admission, probably secondary to frequent vomiting. Another argument in favor of discontinuing the use of these measures is the results of experiments conducted by Bragdon on 77 patients including normal controls. Solutions used were 50% dextrose, 50% sucrose, sorbitol, 10% sodium chloride and caffeine sodium benzoate. It was found that these solutions had little effect on normal individuals and in most of those with increased intracranial pressure there was a moderate drop in pressure for one to two hours followed by a secondary rise above the original pressure. In general the results were unpredictable and in a few cases, a progressive rise in intracranial pressure occurred.

In only 38 cases was therapy directed to keeping the patient in a normal state of hydration to combat the effect of vomiting and inability to take fluids orally.

TREATMENT—SURGICAL—16

Elevation depressed fracture	7
Drainage brain abscess	1
Evacuation extra-dural hematoma	1
Evacuation sub-dural hematoma	1
Wound debridement	1
Rt.-parietal trephine	1
I & D of scalp abscess	1
Lft. trans-temporal decompression	1
Aspiration hematoma scalp	1
Suture laceration	1

FIG. 2

Spinal taps were done in 4 in an attempt to partially reduce the increased pressure. It is important to obtain pressure readings and draw off the fluid slowly to prevent too rapid a decompression from below. It is questionable if such a precedure should be done in patients exhibiting signs of severe cerebral edema.

Other measures consisted of anti-convulsants and sedatives for restlessness, phenobarbitol being used most frequently (in 70). It should be stressed here that the use of morphine and its derivatives is contraindicated in head injuries. In prevention and treatment of infection the sulfonamides and more recently penicillin were used in 19 cases. Stimulants prescribed in terminal cases, oxygen in 2 cases, plasma and blood for the prevention and treatment of shock in 7, and antipyretics in 19 cases.

Surgical treatment was resorted to in 16 cases. Operative procedures done early included; drainage of a brain abscess, evacuation of an extra-

dural hematoma, wound debridement, right parietal trephine and a left trans-temporal decompression. Delayed operative therapy included elevation of a depressed fracture in 7 cases and evacuation of a sub-dural hematoma, incision and drainage of a scalp abscess, aspiration of a scalp hematoma and suture of a laceration in one case each.

Prognosis

We can report on relatively few of the patients who were followed after discharge from the hospital in view of the absence of clinic records on the private patients; therefore the 3% incidence of residual symptoms is misleading. Six percent of 36 patients admitted during the past two years had residual central nervous system involvement and may be considered a significant figure as all but a few of these children were followed in the neurological clinic. Neurological signs were present in 10 cases, major convulsions in 1 case and persistant headaches in 1 case. There were 5 deaths in our series, or a mortality rate of 1.5%. Eighty cases of skull fracture reported by Children's Memorial Hospital in Chicago showed a mortality rate of 2.5%. Our incidence of deaths in a comparable series of 83 skull fractures was 6.0%.

The deaths in this series are briefly:

1. A 7 year old colored female was admitted with history of a fall and striking the back of her head on the pavement. There was no loss of consciousness. She became semi-comatose a few hours after admission, rapidly progressing into deep coma and expired 29 hours after admission. The spinal fluid showed the presence of blood.

2. A 19 month old infant who fell three stories received multiple fractures of the skull and on neurological examination showed flaccidity of all extremities, no response to pain and fixed non-reacting pupils. Death occurred in two hours.

3. A 2 year old child with a history of a fall from a 2 story dwelling presented on admission flaccid paralysis of the right extremities and elevation of temperature, pulse and respiration. She did not regain consciousness and expired 48 hours after admission.

4. An 8 year old boy was struck by an automobile, became unconscious immediately and on entry was comatose with dilated non-reacting pupils and generalized spasticity. The blood pressure which was elevated to 135/80 dropped to 50/0 one hour before death. He died 7 hours after admission.

5. This was the previously described case of meningo-encephalitis secondary to fracture of the cribiform plate.

Summary

In summary 323 patients with head injuries have been admitted to this hospital during the past 5 years. A study of their hospital course demonstrates the importance of careful clinical observation with special reference to detailed history, records of neurological signs on admission and on succeeding days, frequent readings of blood pressure and pulse rate in severe injuries, the prevention of acidosis, dehydration and infection, and conservative "watchful waiting" on the management of these patients.

Special Report

STREPTOMYCIN

Dr. Donald G. Sharbaugh*

Antibiotic agents of microbial origin have been obtained from three general sources:

1. Antibiotic agents of bacterial origin (non spore forming or spore forming bacteria), the most important of which is tyrothricin.
2. Antibiotic agents derived from molds and fungi, the most important of which is penicillin.
3. Antibiotic agents originating from actinomycetes of which the most promising appears to be streptomycin, first described by Schotz, Bugie and Waksman in January 1944.

A closely related substance, streptothricin, derived from actinomyces lavendulae, previously had been described by Waksman. While streptothricin was isolated from a soil actinomyces identified as actinomyces lavendulae, streptomycin was obtained from a strain of actinomyces which was similar in cultural characteristics as well as morphology to a strain of actinomyces griseus which had been described some 25 years before by Waksman. While streptomycin resembles in some respects streptothricin, it is evident that it differed in that it possessed a greater activity against various gram negative bacteria. The name "streptomycin" was given to this substance by the group of investigators from Rutgers University because the substance was produced by one of the aerial-mycelium producing and sporulating group of actinomycetes. To this group of actinomycetes had been given the generic name streptomyces by Waksman and Henrici in 1943. Streptomycin was obtained from filtrates of mediums in which actinomyces griseus (sutiable strains) had been allowed to grow for a period of 5 to 12 days.

The potency of streptomycin, like that certain other antibiotic agents such as penicillin, is described in terms of units of antibacterial activity as measured by the inhibition produced by the substance against a test organism. A unit of streptomycin as described by the investigators at Rutgers University, is that quantity of the antibiotic agent which inhibits the growth of a given strain of Escherichia coli in one ml. of nutrient broth or agar. Streptomycin is a fairly stable substance and is readily soluble in water. Furthermore it was evident from the report of Jones and Waksman and others that experimental animals treated with streptomycin could be

* This essay was submitted in competition for the Mead Johnson Prizes which are to be awarded to members of the fourth year class of George Washington and Georgetown Medical Schools for excellence in Pediatric theses.

protected against lethal infections produced by susceptible gram negative pathogens and there appeared to be little or no evidence of toxicity following the administration of therapeutically effective amounts of this material.

Absorption of Streptomycin with Various Routes of Administration

Oral administration: Patients given streptomycin per oral showed a striking reduction in the number of E. coli as well as other organisms present in the fecal stream occurs. Studies indicate that streptomycin cannot be demonstrated in the blood stream when patients receive as much as 5,600,000 units of streptomycin per day by mouth. Likewise the excretion of streptomycin in the urine was negligible in a period of 24 hours. It appears, therefore, that streptomycin is not absorbed from the bowel when given in dose of 600,000 units or less daily. A solution containing 20 units of streptomycin per c.c. was incubated at 37 degrees for 3 hours with an equal volume of gastric juice containing free hydrochloric acid. Assay of the mixture at the end of the period of incubation showed that the exposure to gastric juice for 3 hours had resulted in no loss of the drug's activity.

Intravenous administration: The following figures will show the concentration of streptomycin in the serum following intravenous injection. Conclusions that can be drawn are:

1. Highest levels were obtained 5 minutes after injection.
2. Levels are in proportion to the amount injected.
3. Concentration in serum decreases rapidly during first hour but in succeeding hours, fall is more gradual.
4. Theoretically the continuous intravenous method of administration would be the method of choice.

Intramuscular injection: Heilman and others believe under most clinical circumstances, probably intramuscular administration is the method of choice at present. Reasonable concentrations are maintained in the blood for at least 3 hours after administration, by this method, of adequate doses of streptomycin. In some instances antibacterial amounts of streptomycin will be found to remain in the blood 4 to 6 hours after last injection. Anderson and others believe that the only essential difference between intravenous and intramuscular administration was the concentration in the serum after 5 minutes after intramuscular injection were much lower. The levels at other times were about equal and the persistence of the drug in the serum after a given dose did not vary significantly with the route of administration.

Subcutaneous administration: 1. Preparations of highest potency can be injected subcutaneously every 3 hours with less discomfort than when any other method of administration is used.

2. It may produce some pain and local irritation at the site of injection.

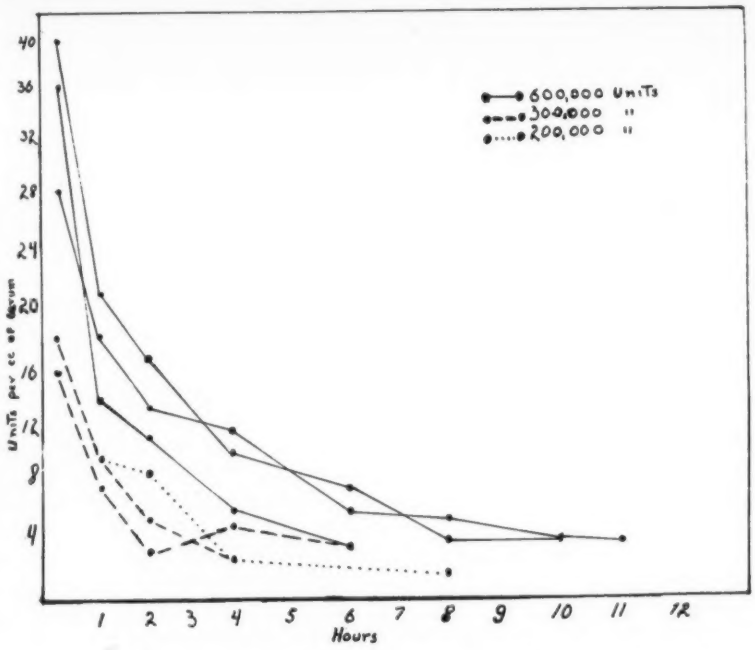

FIG. 1. CONCENTRATIONS OF STREPTOMYCIN IN SERUM FOLLOWING THE INTRAVENOUS INJECTION OF VARYING DOSES

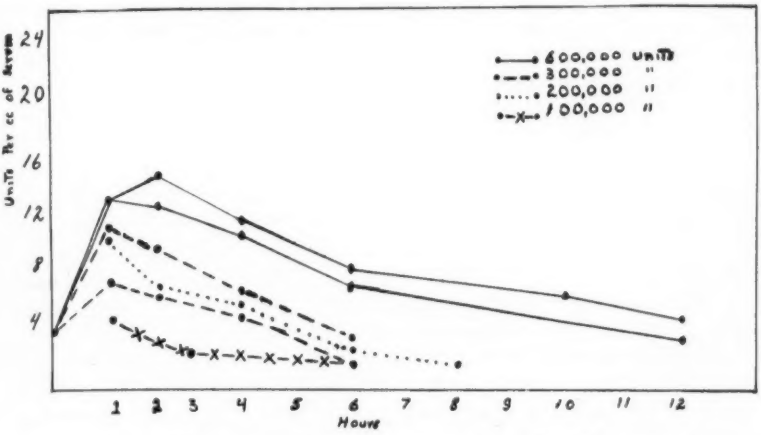

FIG. 2. CONCENTRATIONS OF STREPTOMYCIN IN SERUM FOLLOWING INTRAMUSCULAR INJECTION OF VARYING DOSES

3. Reasonable antibacterial amounts have been maintained in the serum following subcutaneous administration.

4. One advantage of this method of administration is that highly trained personnel are not required.

Intrathecal administration: Single injections of as much as 100,000 units of streptomycin dissolved in 10 c.c. of physiological saline solution, have been administered intrathecally for meningitis. No evidence of serious outward reactions has appeared. Antibacterial amounts of the substance have been found in the cerebralspinal fluid for at least 24 hours after these injections.

Diffusion into cerebralspinal fluid: Studies of the diffusion of streptomycin from the blood into the spinal fluid were carried out in a patient with meningitis. The cerebralspinal fluid was tested for its streptomycin content on 4 separate days at intervals varying from 2 to 8½ hours after parenteral administration of doses of 200,000 and 300,000 units of streptomycin. Simultaneous serum levels were determined, and by coincidence were 5 units per c.c. on each occasion. On 2 days the spinal fluid showed merely a trace of streptomycin, whereas on the other 2 days readings of 1 unit per c.c. were obtained.

Diffusion through the placenta: Varying amounts of streptomycin were administrated before the time of delivery. The interval of time between the last dose and the time of delivery varied from 45 minutes to 2½ hours. In some instances single injections of streptomycin were carried out and in some instances repeated injections were given before time of delivery. Blood was obtained from the mother at time of delivery and specimens of blood from the umbilical cord were obtained simultaneously. Streptomycin traverses the placenta and is readily available in the fetal circulation. The concentration of streptomycin in the blood of the umbilical cord appears to vary somewhat, depending on the dose and the time which elapses between the last injection and birth.

Excretion of Steptomycin

Streptomycin in bile: Studies on excretion of streptomycin in bile are incomplete but are sufficient to indicate that the material apparently is concentrated and excreted in the bile. A patient received 100,000 units subcutaneously every 3 hours for 5 days. 2 hours after the first injection of 100,000 units, the blood serum contained 6 units of streptomycin per c.c. The concentration in the bile at this time was 12.5 units per c.c.

Streptomycin in urine: The 24 hour excretion of streptomycin shows that excretion is greatest during the first 4 hours after administration, one fifth to one third of the dose injected was not excreted until between the 4th and 12th hour. From the 12th to 24th hour only very small amounts of streptomycin appeared in the urine. From this data it can be concluded

that the urinary excretion of streptomycin is significantly slower than penicillin.

Consideration of Toxicity

Irritation of the site of injection: Local irritation may occur occasionally following administration of streptomycin by the intravenous drip method. Actual thrombosis rarely has occurred; however, often it is necessary to change the site of injection frequently. Pain at the site of subcutaneous or intramuscular injection also may occur, especially when streptomycin of low potency is used. The discomfort is described as a burning sensation and usually of short duration.

Chills and fever: Occasionally chills and fever have occurred following the administration of streptomycin. The reaction is similiar to the one encountered with the administration of penicillin which is not pyrogen free. More frequently a slight elevation of temperature is noted, which is of no significance.

Cutaneous toxic manifestations: At times generalized flushing, not unlike that seen in association with a histamine reaction has been observed in cases in which relatively impure streptomycin has been administered. Likewise, dermatitis (toxic erythema) and cutaneous eruptions of an urticarial type have occurred following administration of streptomycin as it is available at present for clinical use. Although streptomycin may be continued in the presence of these eruptions, it is important to remember that severe dermatitis may result.

Joint pain: Several patients who received streptomycin complained of severe pain in the joints and muscles of the extremities. Such patients usually exhibited fever and other evidence of intolerance for the substance.

Nausea: A few patients who recived streptomycin and who exhibited one or more of the aforementioned reactions complained of nausea and, on occasions, they had vomited.

Effects on Liver, Kidneys and Blood

Liver function: No conclusive evidence has been presented of interference with hepatic function following the use of streptomycin.

Renal function: All patients who received streptomycin were carefully studied with regard to possible impairment of renal function. Determinations of blood urea were made frequently. In no instance was there a rise in blood urea. Likewise, urea clearance tests did not reveal any significant change; in fact as much as 150,000,000 units of fairly potent streptomycin has been administered over a period of 42 days to a single patient who had a solitary kidney (average daily dose approximately 3,500,000 units) without evidence of interference with renal function.

On the other hand repeated large doses of streptomycin at times have been followed by evidence of renal irritation. For example, a patient received 400,000 units intravenously every 3 hours for 3 doses, albuminuria and microscopic hematuria developed; however, no evidence of permanent renal damage followed cessation of administration of the substance.

Hemolytopoietic system: Determinations of hemoglobin content were made frequently and erythrocyte, leukocyte and differential blood counts were made before, during and after administration of streptomycin. Likewise, blood smears were examined frequently for evidence of any morphological change after short or prolonged treatment with streptomycin. In no instance had any effect been noted which could be attributed to the preparation.

Case Reports

Effect on tularemia in mice: Lethal infections owing to Pasteurella tularensis were established in mice. Of 30 untreated mice, all died of tularemia within 96 hours after inoculation, a mortality rate of 100%. 30 mice received 1,000 units each of streptomycin per day for 10 days. All 30 survived. Of 12 additional mice that received only 500 units per day, 5 survived. The protective action of streptomycin on experimental tularemia suggests that this drug may be useful in the treatment of tularemia in man.

Effect on salmonella schottmulleri: 190 units were sufficient to give complete protection to mice weighing 18 to 20 grams against salmonella schottmulleri and also Pseudomonas aeruginosa.

Effect on brucella abortus: 15 day old chick embryos were used. A relatively small number of bacterial cells were injected into each embryo. The streptomycin was a crude liquid preparation containing 100 mg. of dry ash free material per milliliter. Excellent protection was afforded by streptomycin. Complete protection in experimental animals was also obtained against Proteus vulgaris.

Effect on meningitis due to hemophilus influenza: A 5 year old girl had a meningitis and bacteremia due to H. influenza. After 8 weeks of treatment with sulfadiazine and sulfamerazine, the patient was still acutely ill and cultures of the blood and spinal fluid were still positive. Streptomycin was started, the patient receiving a total of 2,725,000 units intramuscularly and 255,000 units intrathecally over a period of 3½ weeks. There was a prompt clinical and bacterological response and the patient completely recovered.

Effect of streptomycin on bacteria commonly found in urinary infection: As has been shown by Waksman and his associates, streptomycin has strong bactericidal action on both gram negative and gram positive bacteria, including practically all of those found in urinary infections. Its striking

effects on Pseudomonas aeruginosa which is most resistant to urinary antisepsis, makes its usefulness almost certain. The following table will give some evidence of the above statement:

*Bacterial effect of various concentrations of streptomycin on large innoculations of bacteria**

BACTERIA	ORGANISMS PER 0.5 CC.	UNITS OF STREPTOMYCIN PER CC. URINE				
		12	46	70	117	147
Aerobacter aerogenes	36,000	0	0	0	0	0
Escherichia coli	40,000	+	0	0	0	0
Staphylococcus aureus	24,000	+	+	0	0	0
Proteus ammoniae	40,000	+	+	+	+	+
Pseudomonas aeruginosa	12,000	+	+	+	+	+
		117	176	235	470	587
Streptococcus fecalis	20,000	+	0	0	0	0
	6,000	0	0	0	0	0
Pseudomonas aeruginosa	24,000	+	+	0	0	0
	60,000	0	0	0	0	0

* Effects determined by result after 72 hours inoculation.

Effects of streptomycin on friedlander group (Klebsiella): It is evident that streptomycin exerts a marked protective effect on mice infected by intra-abdominal injection of Klebsiella. 49 out of 60 mice lived when treated with 185 to 500 units of streptomycin per day. All untreated mice died.

2 patients who had Klebsiella infection of the respiratory tract were treated. In both cases the organism promptly disappeared from the sputum.

Effects of streptomycin on relapsing fever and weil's disease: Streptomycin was found to exert a considerable protective effect on experimental infections produced with Borrilia novyi and eptospira icterohemorrhagiae. Streptomycin was relatively less effective than penicillin in the treatment of these two types of infection. It is suggested that streptomycin may be useful as an adjunct to penicillin therapy in the treatment of spirochetal infections in man.

Effect on tuberculosis: Impressions obtained from the study of 34 patients who had tuberculosis and were treated with streptomycin during the past year, it appears probable that streptomycin has exerted a limited suppressive effect, especially on some of the more unusual types of pulmonary and extra pulmonary tuberculosis in this small series of patients. While the reproduction of Mycobacterium tuberculosis may have been temporarily inhibited by the treatment administered, no convincing evidence of rapidly effective bacterial action was obtained.

As long as streptomycin remains difficult to procure and the toxic effects of protracted treatment remain in doubt, it would appear inadvisable to utilize it in treatment of some of the commoner forms of chronic pulmonary tuberculosis in which patients are not likely to derive a striking benefit. During this time emphasis should be placed on the study of early and extensive hematogenous forms of pulmonary tuberculosis, tuberculosis of the genito-uninary tract, suppurative tuberculous lymphadenitis and early miliary tuberculosis.

Effect of streptomycin on typhoid: Streptomycin, when injected intravenously or intramuscularly in doses of from 1,000,000 to 4,000,000 units daily appears in the blood and urine in patients with typhoid in amounts theoretically sufficient to kill E. typhosa. Small quantities are excreted in the feces. When given orally, only traces appear in the blood and the urine, and most of it is excreted unchanged in the feces in quantities excessive to suppress E. typhosa and E. coli. Both parenteral and oral therapy seem to be desirable in treating typhoid, the one to control systemic and urinary tract infection, the other to sterilize the feces, to prevent reinfection and to avoid the carrier state. There is evidence that different strains of E. typhosa vary in their resistance to streptomycin, but there is no evidence here of the development of increased resistance to streptomycin during exposure to it in the body.

Of 5 patients treated parenterally with streptomycin, recovery took place in 3 during treatment.

Summary and Conclusions

1. Streptomycin is not absorbed after oral administration in amounts sufficient to produce detectable concentration of the drug in the serum.

2. The failure of the drug to be absorbed from the gastro-intestinal tract is not due to the inactivation of streptomycin by gastric juice.

3. Intravenous and intramuscular injections do not differ in serum concentration except during the first few minutes after injection.

4. Following intramuscular and intravenous administration 46 to 87% of the dose injected can be found in the urine in 24 hours.

5. Streptomycin is excreted more slowly than penicillin. It appears likely that effective blood levels can be maintained by injections at 6 to 8 hour intervals.

6. There is only slight if any diffusion of streptomycin from the blood into the cerebralspinal fluid.

7. The intrathecal administration of streptomycin in doses up to 20,000 units does not produce signs of meningeal irritation. With doses of 16,000 to 20,000 units, and appreciable concentration of the drug can be maintained in the cerebralspinal fluid for at least 24 hours.

8. No serious toxic reactions apparently follow the injection of single doses of streptomycin in amounts up to 600,000 units or after the continued use of the drug for periods of two or three weeks in doses totaling 2,725,000 to 18,150,000 units.

9. The intravenous and subcutaneous injection of concentrated solutions of the present preparation causes too much discomfort to warrant the use of these methods of administration.

10. The drug can be administered in an intravenous infusion without the production of unpleasant symptoms.

11. Intramuscular injections are fairly well tolerated for periods up to one to two weeks. Therapy continued beyone these times may cause severe discomfort.

12. It appears that diffusion of streptomycin takes place through the placenta and that streptomycin is available in the fetal circulation. Streptomycin also appears to be concentrated and excreted in the bile.

13. Streptomycin should prove to be the most useful urinary antiseptic so far developed.

14. The effects of streptomycin on H. influenza meningitis, tuberculosis, tularemia, brucellosis, Weil's disease, typhoid and Friedlander Group. May well afford an effective cure in the near future.

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Special Report

ADVANCES IN IMMUNIZATION IN PEDIATRIC PRACTICE

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In recent years it has been recognized that nearly all primary immunization procedures, in order to obtain optimum effectiveness, should be given from the sixth to twelfth months of life. As a result it has become a generally accepted procedure in pediatric practice to start immunizing measures at the sixth or seventh month. However, recent work has indicated that under some circumstances certain procedures should and can be initiated even before the infant has reached the age of six months. For example, in the event of a smallpox epidemic, infants should be vaccinated very shortly after birth, and where there is imminent danger of pertussis, vaccine may be given in the fourth month or even earlier.

Every child is entitled to protection against three diseases—smallpox, pertussis, and diphtheria. If circumstances indicate, active immunization for scarlet fever, typhoid fever and tetanus may be given. Recent advances have been made in our knowledge of pathogenic bacteria as antigens and in the nature and immunologic properties of viruses. This new knowledge has led to the development of several new methods for the production of active immunity. It will be the purpose of this paper to review briefly such procedures as are now routinely used and comments on certain changes which may be made in some of them in the light of recent investigations and those now in progress.

Smallpox

Calf vaccine virus is still the method of choice in the oldest of the immunization procedures, first established by Jenner in 1798. Rivers[1] and his coworkers have suggested the use of tissue-culture virus and have obtained good immunizing results. Being bacteria free, this preparation has the advantages of allowing intradermal inoculation. It produces no open lesion liable to pyogenic infection and gives immunity without the production of a scar. Because it has not yet stood the test of a smallpox epidemic, this method has not been accepted universally by health officers[2]. However, it will probably be more widely used in the future. Vaccine virus propagated in the developing hen's egg has also been suggested as a substitute for calf lymph. Neither of these preparations, however, has proven superior to the tried and true calf vaccine virus, and this product is in general use at the present time.

The scratch method of vaccination, which was popular at one time, has gradually been replaced by the multiple acupuncture or multiple pressure

* Student thesis.

method. The skin is prepared with acetone, preferably at the insertion of the deltoid of the left arm, a drop of vaccine of high potency which has been kept at or near freezing temperature is placed on the site, and the vaccine is introduced into the epidermis by pricking the skin through the drop with a sterile needle held parallel with the surface of the skin. The needle is pressed against the skin fifteen or twenty times, the elasticity of the skin causing the point of the needle to enter the epidermal layer but not deep enough to draw blood. The excess vaccine is then wiped off. A dressing, shield, or occlusive covering of any kind is not used. This method is recommended for routine use by the United States Public Health Service. Nevertheless, other methods, such as the intradermal, crisscross scratch, and scarifying methods are still used.

The intradermal tissue culture virus should probably be used when it is imperative to vaccinate children suffering from eczema orother skin diseases[3].

Smallpox vaccination should be done before the end of the first year. It has been definitely established that reactions are minimal in young infants, and the possibility of post-vaccinal encephalitis is extremely unlikely in this age group. McCoy[4] states that, in his opinion, smallpox vaccination cannot be done too early, but, in any event, should not be postponed later than the age of six months. Smythe[5] concurs in this opinion, saying that the infant may be vaccinated as soon as the cord is off and that the earlier the vaccination the less the reaction will be.

The physician must be thoroughly familiar with the types of reaction which may follow vaccination—primary, accelerated, and immune. Only too often are many repeated vaccinations called unsuccessful only because they have not been inspected at the right time[3]. These reactions are characteristic and because of their importance, they will be reviewed briefly. The primary type passes through the stages of macule, papule, vesicle, pustule and finally scabbing, requiring twenty-one days to complete the reaction. The accelerated or vaccinoid reaction goes through the same stages as the primary type, but its course is completed in about four to seven days. Constitutional symptoms are usually absent and the local skin reaction is negligible. This type of reaction probably indicates incomplete immunity in the individual. The reaction of immunity is manifest by some local induration and redness, occasionally vesiculation, appearing within twenty-four hours from the time of vaccination. This type of reaction should be read within thirty-six to forty-eight hours. In view of its transiency, it is the immune reaction which, if read late, may lead the physician to the false impression of a reaction failure and revaccination of the patient. A true reaction failure is due either to impotent vaccine or an error in technique[5].

In most cases the immunity conferred by vaccination is permanent. However, 10% of individuals will lose their immunity within five years. It is generally agreed, therefore, that re-vaccination should be done when the child enters school and again at about the age of twenty or twenty-five. If the disease is prevalent, it is usually a safe rule to vaccinate every person who has not been successfully vaccinated within five years. Vaccination should be done each time there is an exposure, according to Toomey[6], in view of the fact that there may be a reaction of immunity five or six years after vaccination and yet the individual may lose his protection the very next year.

Pertussis

In early infancy whooping cough is one of the most fatal of the infectious diseases, and its greatest mortality rate is in infants under the age of one year. It is these children who should be protected if at all possible.

At the present time the vaccines of choice are those of Sauer and Kendrick and other similarly prepared vaccines. These preparations have withstood the clinical test of time.

It has been estimated that about 80% of children who have been intimately exposed to pertussis will contract the disease, while of those who have been immunized, only about 15% develop whooping cough when similarly exposed, and in practically all of these the disease runs a mild course.

The present method in using Sauer's vaccine (fifteen billion organisms per cc.) is to give three doses of 2 cc., 2.5 cc., and 2.5 cc. subcutaneously at three week intervals, starting any time after the sixth month. It has been the practice to wait until the sixth month because of the belief that young infants do not possess the ability to develop an active immunity. It appears, nevertheless, that although newborn babies have a high degree of resistance to such diseases as scarlet fever, diphtheria and measles, they are susceptible to whooping cough from the day of birth. It is difficult to explain the apparent lack of immunity to whooping cough when the child probably derives a passive immunity to the other infectious diseases by the transfer of maternal antibodies through the placental barrier. Kendrick, Thompson and Eldering[7] recently conducted a study of the placental transfer of circulating antibodies to pertussis by comparing the opsonocytophagic reactions of two groups of mothers and their newborn infants. One group of women received a series of pertussis vaccine injections during the latter months of pregnancy in order to raise the level of immunity, while the second group received no vaccine. It was shown that the immunized mothers showed twice the opsonic activity of the non-immunized group, while the babies of vaccinated mothers had three times the opsonic activity

of the babies whose mothers received no vaccine. It was the conclusion of these investigators that the pertussis circulating antibodies do pass through the placenta and that the higher the level in the mother, the more nearly does the baby's titer approach her own. It was not suggested that this procedure confers an adequate passive immunity to give the baby a high degree of resistance to pertussis.

Several studies[8,9,10,11] have been made in the past several years to determine whether or not alum precipitation of pertussis vaccine might increase its antigenic efficiency such as was found to be the case in diphtheria toxoid. It was generally concluded that this vaccine conferred real protection and is as effective as a standard vaccine of the same strength, judging by complement fixation reactions.

Sako, et al.[12], after studying early immunization against pertussis with alum precipitated vaccine, suggested that protection against whooping cough as early as two to twelve weeks of life is a practicable procedure.

Recently, Garvin[13] studied the efficacy of whooping cough vaccine by comparing the incidence of pre-school pertussis in two adjacent cities—Shaker Heights and Cleveland, Ohio. The former had almost 75% of its pre-school population immunized against whooping cough while the latter had an immunization percentage of about 10%. There was such a great difference in the incidence of pertussis in the two cities that it was his conclusion that prophylactic immunization against pertussis should be as standard a procedure as protection against smallpox and diphtheria.

Promising results have been shown in recent studies by Strean and others[15, 16, 17] on new skin testing techniques as a simple index of immunity to pertussis. Felton and Willard[18] state in their review of prophylaxis by Hemophilus pertussis vaccine that the control of whooping cough will be greatly simplified should the results of these methods continue to be satisfactory.

Diphtheria

Diphtheria toxoid immunization probably ranks next to smallpox in importance and should be carried out on all susceptibles under the age of ten years, preferably in the second six months of life. The preventive measures which have been developed against diphtheria are, in a large part, responsible for the gradual reduction of the amount of this disease throughout the world. However, diphtheria is still far from being wiped out[19].

The Schick test is very specific and indicates sensitivity to diphtheria toxin when positive. During the first six months of life there may be enough passive immunity from the maternal circulation to prevent a positive Schick test, and for this reason, it is usually valueless in this age group, for it does not reflect the true condition of the infant's resistance. Inas-

much as this passive immunity is lost within the first year of life, it is a wise procedure to immunize routinely all children before the end of the first year, preferably at the seventh month, regardless of the Schick reaction.

Active immunization is carried out by injecting diphtheria toxin in modified form. However, there is some difference of opinion as to whether one should use the plain or the alum-precipitated toxoid. In children under six years of age toxin-antitoxin mixtures have been largely discarded in favor of the toxoids because of the undesirable effects of the foreign serum proteins in the former. Muenekens[3] favors the use of the plain toxoid, which he gives subcutaneously at monthly intervals in three doses of 0.5 cc., 1.0 cc., and 1.5 cc. Alum-precipitated toxoid is usually given in two doses of 1.0 cc. each and has the definite advantage of fewer injections.

After the age of six years, reactions to the diphtheria toxoid preparations are usually more severe, and those who are Schick positive should be immunized with toxin-antitoxin[2].

Immunity should be assayed from four to six months after immunization by the Schick test. A negative test usually indicates that the child is immune, while, conversely, if a positive result is obtained, one should renew his efforts to produce an active immunity.

Because the response to active immunity in children below six months of age is generally regarded to be poor, those who are exposed to the disease should be protected with 1000 units of antitoxin at once. This confers an immunity for two or three weeks. That the infant may derive little protection from passive antibody transfer from the maternal circulation is demonstrated in a case reported by Smith[20] of diphtheria in a nineteen-day-old baby of a mother who was found to be Schick negative.

A new phase in diphtheria control has recently come to light. It has been recognized that due to the remarkable efficiency of artifical immunization procedures in decreasing the prevalence of diphtheria, natural resistance to the disease has decreased, and, as a result, levels of artificial immunization which were once adequate to protect a community may no longer suffice[21]. Schwartz and Janney[22] predicted this condition in 1938. It has been suggested that the continuation of diphtheria immunity be assured by the administration of activating doses of diphtheria toxoid at yearly intervals during the pre-school years when there is the greatest susceptibility to this disease[23]. Bousfield[24] has demonstrated that diphtheria immunity can be maintained without injection through the use of toxoid pastilles by mouth. His rationale for this procedure takes into consideration the fact that the toxin of the disease is presumably absorbed from the mucous membranes in the upper respiratory tract. His results, however, have not been verified, and much work yet remains to be done on the applicability of this method.

Scarlet Fever

Although active immunization to prevent scarlet fever has been recommended, this method of protection has not been accepted universally and is being used less and less each year. This is due in part to the fact that the scarlet fever toxin protects the individual only against the erythrogenic exotoxin of the scarlet fever streptococcus, offering no protection against the endotoxin. Also, such immunization does not eliminate the individual as a source of infection to others and the immune person may suffer from a "strep throat" without presenting clincal evidence of scarlet fever; i.e., "scarlatina sine exanthem." Furthermore, according to the method advocated by the Dicks, it is necessary to give a minimum of five doses at weekly intervals, some of which may be followed by severe reactions. Finally, there is some question as to how long the immunity lasts.

Such are the factors which restrict the widespread use of immunization in scarlet fever. Nevertheless, this procedure is not to be entirely discarded for it is a valuable prophylactic aid in times of epidemics.

If the mother is immune, the infant usually acquires a passive immunity, which generally disappears during the first year of life. The Dick test for susceptibility to scarlet fever will change from negative to positive at this time.

Of the several methods advocated to produce active immunity, the Dick method of the subcutaneous injection of gradually increasing doses of toxin has given the best results[19]. A commonly used dosage schedule is as follows:

1st week	500 S.T.D.
2nd week	2500 S.T.D.
3rd week	20,000 S.T.D.
4th week	40,000 S.T.D.
5th week	80,000 S.T.D.

Dick and Dick define a skin test dose (S.T.D.) as "the amount which gives positive reactions in persons susceptible to scarlet fever and negative reactions in persons immune to the disease."

Active immunization may be instituted in infants over twelve months of age. Reactions are less severe in these younger patients, and they are further minimized in severity and frequency by reducing the dose and extending the course to seven or eight injections, gradually increasing the dose[25, 26]. Smythe[5] suggests determining the sensitivity to scarlet fever toxin by the Dick test and reducing the first dose in proportion to the intensity of the reaction, followed one week later by instituting the regular course suggested by the Dicks.

Scarlet fever pooled convalescent serum and scarlet fever antitoxin have

been found useful in both the passive prophylactic immunization of exposed children and in the treatment [27] of this disease.

Typhoid Fever

Typhoid fever vaccine has been found to be efficient for active immunization. It may be given during epidemics and should be given routinely to individuals usually above the age of two who live in localities where typhoid fever is endemic or where the water supply is questionable. Likewise, it should be given to travellers whose journeys take them through places where the water supply may be contaminated. It is also recommended in persons who have been exposed to typhoid fever [6].

Although at the present time it is common practice to use the so-called triple vaccine, consisting of a suspension of E. typhosus, S. paratyphosus A. and S. paratyphosus B., pure typhoid vaccine consisting of one billion organisms per cc. is to be preferred in children [2]. The vaccine is given in three weekly doses of 0.5, 1.0, and 1.0 cc. One-half of this dose is used in children under two years of age. Immunity is only relative and is considered adequate for a period of three years.

Siler and his coworkers [28] at the Army Medical School have shown that a "booster" or stimulating dose of 0.1 cc. of the vaccine intradermally effectively restores the antibody level and so presumably maintains resistance. In endemic areas it may be well to give "booster shots" every year, a routine adopted by the Navy.

In general, children show less constitutional reactions than do adults; however, Enders [29] states that intradermal inoculation is usually attended by reactions of less intensity as compared with the technique of subcutaneous injection, and that inasmuch as the antibody response is excellent, this method should come into general use in the near future.

Tetanus

In the armed forces active immunization against tetanus is a routine procedure and has been responsible for saving thousands of lives. In civilian practice, however, the problem may be considered slight from the standpoint of the general public health, and tetanus toxoid alone is not routinely given unless the child lives in an environment or is engaged in such activities as are likely to predispose him to this dangerous disease. Furthermore, it has been suggested that all allergic children should be actively immunized since many of them would likely be sensitive to horse serum [30]. Some authorities recommend routine active immunization against tetanus, and this is becoming more widely accepted since the advent of the combined immunization procedures.

The toxoid may be administered in its original fluid state by three sub-

cutaneous injections of 1.0 cc. at three to four week intervals, or it may be given as the alum-precipitated form in two doses of 1.0 cc. each intramuscularly at a two- to three-month interval. There is no conclusive evidence that reactions are greater in the precipitated form, and the administration of only two doses is a distinct advantage over the fluid toxoid. A stimulating dose should be administered at the time of exposure to a possible tetanus infection. The fluid toxoid is preferable at this time because it is absorbed more rapidly than the alum-precipitated toxoid with a more rapid rise in circulating antitoxin.

Unimmunized children should be given passive prophylaxis using tetanus antitoxin intramuscularly in doses of from 1000 to 2000 units. This procedure should always be preceded by a skin test to determine the existence of hypersensitivity to serum.

Immune Globulin in Measles

Gamma-globulin is a by-product of plasma fractionation and was recently found a safe and effective agent for the prevention and modification of measles[31]. This preparation (fraction II of Cohn, Strong, Oncley, Hughes and Armstrong[32]) contains antibody globulins which are standardized so that the concentration of the antibody is twenty-five times that of the plasma pool from which it came.

This preparation may be used either for the prevention or modification of measles by passive immunization and is the safest and most effective agent available for this purpose. In order to prevent the disease, a dose of 0.075–0.1 cc. per pound of body weight as soon as possible after contact is suggested. On the other hand, a dose of 0.02–0.025 cc. per pound on the fifth day following definite exposure will result in mild measles in most cases with the production of a subsequent lasting immunity. The decision as to whether a child should be completely or partially protected is left to the individual physician to decide. The material is injected intramuscularly.

Reactions are very rare, Janeway[33] reporting an incidence of 1.7 per cent of 1,843 intramuscular injections, half of which consisted only of local soreness and most of the remainder of slight fever.

A single dose will probably protect a child for about three weeks. The modified form of measles which results from a proper "modifying dose" of gamma-globulin is apt to be one in which the fever and malaise are greatly diminished, the catarrhal symptoms slight and the rash evanescent and sparse[34].

Gamma-globulin is extremely useful in controlling outbreaks of measles in pediatrics wards and is of great value because of the contagiousness of this disease. However, preliminary studies indicate that it is of little value in protecting against another highly contagious disease which may threaten ward patients, chickenpox[32].

Other preparations advocated for use in measles prophylaxis, such as convalescent serum, normal adult serum and placental globulin extract, have not shown as great effectiveness as gamma-globulin [32].

Multiple Antigens

The practice of simultaneous immunization against more than one disease, using multiple antigens, has recently come to the fore and offers certain advantages. It not only contributes to administrative economy and efficiency, but there is some evidence to indicate that the immune response to combined antigens is often greater against each than when single antigens are injected [25].

The most widely used of these combined immunization procedures is that against diphtheria and tetanus. Many physicians who would not ordinarily immunize against tetanus now do so routinely along with diphtheria immunization through the use of combined diphtheria and tetanus toxoids. Other combined antigens in wide usage are: diphtheria toxoid and pertussis vaccine [53], diphtheria and tetanus toxoids and pertussis vaccine [36]. These combinations have been considered acceptable by the Public Health Study Committee on Multiple Antigens [37]. It is said that reactions from the use of multiple antigens are not appreciably greater than those for single antigens.

With further experience, combined vaccinations may be the future method of choice. The saving in time and the smaller number of injections required as well as the advantages mentioned above are strong arguments in favor of combined immunization procedures.

A routine schedule of immunization in infants, using multiple antigens, may be as follows:

Beginning between six and twelve months of age:

1. 1.0 cc. of alum precipitated mixed antigens (0.5 cc. of standard diptheria toxoid and 10,000 million bacilli per cc. pertussis vaccine).

Three week interval

2. 1.0 cc. of the same as above.

Four week interval

3. Smallpox vaccination.

Twelve week interval

4. Schick test.

The above schedule may also be followed in older children. Active immunity against tetanus may be included along with that for diphtheria and pertussis by using the triple antigen, or the combined diphtheria-tetanus toxoids may be used with the separate injections of pertussis vaccine.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: Dr. E. Clarence Rice
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Case Report No. 40

Dr. Robert B. Sullivan I. K.—41-9771

A two year old colored female was admitted to Children's Hospital on November 6, 1941 because of a swelling in the right groin of three days' duration. The mother vaguely remembered "pulling something out of the child's foot" about one month before admission but the illness was limited to the preceding three days during which a moderate-sized, slightly tender swelling had developed in the right inguinal region. There were no other complaints and she walked and played as usual.

The past history was negative and the parents and eight other children were in good health.

Physical examination revealed a well developed, well nourished child who did not appear acutely ill. The admission temperature was 99.4° rectally and the positive findings were limited to the right inguinal region and the right leg. The inguinal nodes were markedly enlarged, hard, moderately tender, and non-fluctuant. Measurements of the right thigh and calf revealed their circumference to exceed those of the left lower extremity by one inch in the thigh and three quarters of an inch in the calf. The upper portion of the thigh was warm but no localized infection could be found.

The urinalysis was negative. There were 3.4 million red blood cells per c.mm. and the white count was 6,000 per c.mm. with 57% neutrophils and 43% lymphocytes.

Hot wet compresses were applied to the inguinal region for three days during which the child was afebrile and the swelling of the leg receded. She was discharged to be followed in the clinic.

Seven weeks later she was re-admitted because the inguinal nodes had not receded and the swelling of the leg had returned although sulfanilamide and hot compresses had been employed in the interim. Her general condition had remained good. There was marked swelling of the right leg with an increase in the size of the inguinal nodes above and below Poupart's ligament. These appeared to be suppurative but an attempt to aspirate pus was unsuccessful. During this admission the temperature ranged between 98.0° to 102.8°.

The laboratory data was as follows: Urinalysis was negative; red blood count was 3.24 million per c.mm.; white blood count was 13,400 with 45% polymorphonuclear forms and 55% lymphocytes; tuberculin, Kahn and

agglutination tests for B. melitensis and P. tularensis were all negative; blood examination for filaria was negative; x-ray examinations of the chest, spine, pelvis, right hip and leg were all negative; x-ray examination of the colon by means of a barium enema indicated a displacement of the cecum upward with distortion of the normal architecture about the caput possibly due to pressure from without or invasion of the wall.

After two weeks of hospitalization there developed a marked induration, with little tenderness, extending from the groin upwards toward the umbilicus in the right lower quadrant. A moderate left inguinal and axillary lymphadenopathy was found to have developed. X-ray irradiation was directed to the right groin but a course of four treatments caused no change. Biopsies were obtained from the left and right inguinal regions and from the left axillary region. After they were interpreted the child was discharged.

Six weeks later she returned to the dispensary because of labored respirations with some vomiting for three days. She died while being re-admitted.

The duration of the illness was four months and three weeks.

Autopsy summary: The body was well developed and nourished and the right inguinal nodes were numerous, hard, discrete and measured 1.0 by 0.5 centimeters. There were several similar nodes in the left groin. In the right lower quadrant both anteriorly and posteriorly the parietal peritoneum was white and thickened. The retroperitoneal lymph nodes were numerous, firm, closely adhered and measured 1.0 centimeters in diameter. The mucosa of the small and large bowel were studded thickly with tiny white-gray raised nodules. What appeared to be Peyer's Patches were markedly hyperplastic and confluent in the ileum adjacent to the cecum. The gastric wall was invaded by several large, firm nodules of tumor tissue with bright red bleeding surfaces. The entire bowel was filled with bloody mucoid material. On the right the kidney was enlarged with many irregularly shaped bright red areas of new growth but the left contained only a few small neoplastic nodules. The liver showed no gross evidence of metastases and the spleen was normal in size but contained a few large, firm, purple, poorly demarcated nodules of neoplasm. There were numerous metastases to the lungs but more in the right lung than the left. The epicardium was studded with small bright red, irregular nodules extending into the myocardium with the most extensive involvement being in the right auricle. The intracranial contents were not examined.

Pathological diagnosis: Lymphosarcoma.

Discussion

Dr. E. Clarence Rice: This is one of the most interesting sarcomas that we have seen at this hospital.

It has been reported that at the Philadelphia General Hospital this type

of malignacy is the most common in children. This has not been our experience here. Wilm's tumors and neuroblastoma outnumber lymphosarcoma; however, the latter occurs with sufficient frequency as to make it a real possibility when lymphadenopathy is present.

The fact that the patient gave a history of injury, had an enlarged leg, fever, adenopathy and the lymph nodes failed to respond to irradiation served to make the diagnosis a difficult one. The first biopsy of a lymph node was not diagnostic and indicated a chronic inflammatory condition. The effect of irradiation is ordinarily of diagnostic importance, lymphosarcoma and Hodgkin's lymphogranuloma usually being susceptible to this type of therapy. Neurogenic tumors, in our experience, have not been radiosensitive. Others have had experiences somewhat at variance with ours, as Captain Wyatt at one of our conferences reported a favorable response to irradiation for certain cases of neuroblastoma at the Boston Children's Hospital.

The fibrosis and lack of evidence of any malignancy in the first biopsy may have been due in part to the effect of irradiation, the node having been obtained from the inguinal region where considerable roentgen treatment had been given. The second biopsy was from an axillary lymph node and revealed a very different picture from the first one. Microscopic examination showed a replacement of the usual follicular structure of the node by a solid arrangement of uniform type of cells of the lymphatic series. They appeared to be lymphoblasts. Dr. Lindsay's diagnosis was "lymphoblastoma." This shows that one biopsy is not always diagnostic and that a second may be necessary in order to make a diagnosis.

The necropsy findings are striking with the marked enlargement or formation of masses of lymphoid tissue. Their arrangement is such as to indicate that metastasis took place largely via the lymphatics. While the abdomen contained most of the neoplastic tissue, few parts of the body seemed to have been spared some involvement. In examining the tissue microscopically we find the biopsied lymph node picture was reduplicated in all of the organs involved. One section of the kidney demonstrates the invasiveness of the neoplasm very strikingly. Here we see a few glomeruli and tubules surrounded by a dense mass of lymphoblasts. Another section reveals such marked involvement as to make identification of its source impossible.

Enough has been said to indicate the difficulties which may be encountered in making a diagnosis. Leukemia may have to be ruled out as this disease and lymphosarcoma give similar microscopic findings in the tissues at times. The blood count in children with leukemia oftener is that of leukopenia with a high percentage of blast cells rather than the marked leukocytosis with fewer immature cells often seen in the adult.

Bone marrow aspiration or biopsy may be needed in helping make the diagnosis. A recent case served to bring out new difficulties in the diagnosis of lymph node tumors. This patient with marked cervical lymphadenopathy showed changes in the biopsied node which the pathologist felt were most likely due to tuberculosis. The response to irradiation was sufficient to convince the clinician and roentgenologist that the disease was Hodgkin's lymphogranuloma. However, the patient died of histoplasmosis, another disease which we will have to consider in the future when we find enlargement of the lymph nodes.

This case is illustrative of the necessity of considering all of the evidence at hand rather than relying too much on any one finding or diagnostic aid.

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